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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/001,278	11/01/2001	Robert V. Farese JR.	407T-927110US	2111

22798 7590 04/10/2003

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	6

DATE MAILED: 04/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/001,278	FARESE ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *12-26 and 38-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 27-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 8, dated 02/20/2003 is acknowledged. The traversal is on the ground(s) the double knockout animals of Groups II and III are dependent to the generic claims of Group I and that to search Groups I-III together would not be a burden. The animals of Groups I-III are genetically, structurally, functionally and phenotypically distinct. They have a different purpose and require additional search as they relate to the disruption of additional genetic loci, additional phenotypes, and additional uses. The burden required to search Group I with either or both of Groups II and III would be undue. The requirement is still deemed proper and is therefore made FINAL.

Claims 12-26 and 38-56 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) in Paper No. 8. Claims 1-11 and 27-37 are currently under consideration.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The claimed invention is directed to non-statutory subject matter. Claims 1-11, as written, encompass a human, which is non-statutory subject matter. Changing claim 1 to read non-human knockout mammal would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 27-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 27 encompass more than one *Ttpa* gene as they are drawn to "a *Ttpa* gene". The claims encompass any *Ttpa* gene that may exist in each and every species of mammal. The specification does not describe that more than one single *Ttpa* gene is known for any single mammalian species. Therefore, adequate written description to support the claims encompassing more than one *Ttpa* gene in any single species is lacking.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieve regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the *Ttpa* gene disclosed in the specification and its orthologue in other mammalian species, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

Claims 1-11 and 27-37 encompass transgenic knockout mammals produced through gene-targeted insertion in somatic cells followed by generation of animals using somatic cell

nuclear transfer in addition to the more traditional technique of homologous recombination in mouse ES cells followed by transplantation of the ES cell into a mouse blastocyst. The specification prophetically teaches the possibility of using homologous recombination in somatic cells followed by somatic cell nuclear transplantation to generate the claimed animals, however, it does not describe that this technique was actually used to generate the claimed animals or describe, to any degree, the phenotype of said animals. Due to the limited art available at the current time and at the time of publication, it is not clear that knockout animals produced by these two distinct methods would appear the same phenotypically. Fetuses generated by somatic cell nuclear transplantation, irrespective of whether they are genetically modified, are often abnormal and nonviable with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, page 87, column 1, 3rd full paragraph; McCreath, paragraph bridging pages 1067 and 1068). Thus, it would be expected that phenotypes associated with the technique of somatic cell nuclear transfer, of unknown etiology, would arise independent of the phenotypes related to the gene knockout.

Since it is not realistic to expect that the "complete structure" of any transgenic animal can be described, the written description requirement is interpreted to be whether phenotypic consequences have been described. Due to the unpredictability in the art of making transgenic knockout animals and additionally in making animals by somatic cell nuclear transfer, it is not clear to one skilled in the art what the claimed animal would be. Given the limited information in the specification, an artisan would not have been able to predict whether the animals generated by somatic cell nuclear transplantation would have had the same or different phenotypes compared to the animals generated by more traditional methods of homologous recombination in mouse ES cells. Therefore, the limited disclosure in the specification is not deemed sufficient

to reasonably convey to one skilled in the art that Applicants were in possession of all the genera encompassed by the claims.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 27-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for i) a transgenic knockout mouse comprising a homozygous disruption in the endogenous *Ttpa* gene wherein the disruption is an insertion, deletion, frameshift, or stop codon and wherein the mouse exhibits a decreased level of alpha-tocopherol transfer protein, vitamin E deficiency or female infertility and ii) a transgenic knockout mouse comprising a heterozygous disruption in the endogenous *Ttpa* gene wherein the disruption is an insertion, deletion, frameshift, or stop codon and wherein the mouse exhibits vitamin E deficiency, does not reasonably provide enablement for any species of mammal 7comprising a disruption in any *Ttpa* gene wherein the disruption is a substitution and wherein the animal has any phenotype other than a decreased level of alpha-tocopherol transfer protein, vitamin E deficiency or female infertility. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims are directed to knockout mammals comprising a disruption in an endogenous alpha-tocopherol transfer protein (*Ttpa*) gene. Claim 2 limits the species of mammal. Claims 27 and 28 limit the species to a rodent (claim 27) or a mouse (claim 28). Claims 3 and 29 limit the

type of gene disruption and claims 4-7 and 30-33 limit the type of insertional disruption. Claims 8-11 and 34-37 limit the animal to having a disruption in a somatic cell (claims 8 and 34), a germ cell (claims 9 and 35), having a homozygous disruption (claims 10 and 36) or heterozygous disruption (claims 11 and 37).

1) The specification fails to enable making and using any species of mammal, other than mouse, comprising a knockout of the endogenous *Ttpa* gene and fails to enable using any mammal comprising a knockout of the endogenous *Ttpa* gene wherein said mammal exhibits any phenotype. The art at the time of filing held that targeted gene insertion technology was not well-established for any species other than mouse. Since homologous recombination is required for gene targeting methods, cells in culture must be used to carry out the method. To generate an animal from the recombinant cells, the cells must be ES cells capable of contributing to the germ line. Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cell lines that contribute to the germ line in any species other than mouse (page 65). Other potential methods of generating transgenic embryos using homologous recombination had not been fully developed at the time the invention was made (McCreath, 2000, Nature, Vol. 405, pages 1066-1069; Kent-First, 2000, Nature Biotechnology, Vol. 18, pages 928-929; Dinnyes, 2002, Cloning and Stem Cells, Vol. 4, pages 81-90). The first report of gene targeting in a lamb produced by somatic cell nuclear transfer of nuclei using fetal fibroblasts (McCreath, 2000) reported abnormal transgene expression/function. The first knockout lamb using this technique was not reported until after the effective filing date of the instant invention and also met great difficulty (Denning, 2001, Nature Biotechnology, Vol. 19, pages 559-562). Furthermore, cloned fetuses, irrespective of whether they are genetically modified, are often abnormal and nonviable with no consistent pattern of abnormality to indicate the cause of the defects (Dinnyes, page 87,

column 1, 3rd full paragraph; McCreath, paragraph bridging pages 1067 and 1068). It would be difficult to determine whether the phenotype resulting in a genetically modified animal generated by somatic cell nuclear transfer was a result of the genetic modification or an artifact of the nuclear transfer technique.

Furthermore, at the time of filing, the phenotype of transgenic knockout mice was unpredictable. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene that was intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) taught that, despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, at the time of filing, ES cell-generated, gene-targeted animals had not be prepared for any species other than mouse and the phenotype of any species of knockout animal generated via any method was unpredictable.

The specification teaches generating transgenic knockout mice by via insertional disruption of the endogenous mouse *Ttpa* gene using homologous recombination in mouse ES cells. The specification teaches only prophetically, how one would generate a gene-targeted transgenic knockout mammal using cells other than ES cells. However, the specification fails to clearly set forth the methodology necessary to accomplish such an unprecedented task. The specification fails to teach how one of skill in the art at the time of filing would generate a transgenic mammal, including a mouse, comprising a disruption in the endogenous *Ttpa* gene wherein the heterozygous mammal has a phenotype other than decreased levels of alpha-

tocopherol transfer protein or vitamin E deficiency or wherein the homozygous mammal exhibits any phenotype other than decreased levels of alpha-tocopherol transfer protein or vitamin E deficiency or female infertility. It would, therefore, require one of skill in the art at the time of filing, undue experimentation to determine how to make and use any species transgenic mammals exhibiting any phenotype as broadly claimed.

2) The specification fails to enable making a transgenic knockout mammal comprising a disruption in the endogenous *Ttpa* gene wherein the disruption is a substitution. The specification fails to describe where and what nucleotide substitutions would lead to the desired phenotype. Many possible base substitutions will not lead to any detectable phenotypic change at all. Other substitutions, depending on the position within the gene, may lead to different degrees of functional inactivation or over-activation of the gene or gene product. Without a description of where and what types of substitutions would be required to attain the desired phenotype, one of skill in the art would not know how to make and use the claimed mammal.

3) The specification does not enable making and/or using the claimed mammal wherein the disruption is only in a somatic cell or only in a germ cell as encompassed by claims 8,9,34,and 35. It is not clear from the specification how one would reproducibly make an animal comprising the claimed disruption wherein the disruption is only in somatic cells. It is conceivable that one could make chimeric animals that do not pass the gene disruption through the germline. However, the number and location of the cells comprising the disruption would vary between animals. Therefore, one could not make, with any predictability, the animals encompassed by the claims. The art of making transgenic knockout animals is unpredictable because the phenotype attained is unpredictable. Therefore, the level of unpredictability of the phenotype of chimeric animals is even greater. Furthermore, it is not clear from the specification how one would make such chimeras. It is wholly unclear how one would knockout a gene in the

germ line and not affect somatic cells, as encompassed by claims 9 and 35. It is further unclear how one would use these animals. Therefore, it would require one of skill in the art at the time of filing undue experimentation to determine how to make and use an animal comprising a gene knockout only in somatic cells or only in germ cells.

4) The specification fails to enable disrupting any *Ttpa* gene in a mouse or any *Ttpa* gene in any other species. The specification only teaches one mouse *Ttpa* gene. The specification does not disclose that more than one *Ttpa* gene exists in any species and does not provide adequate guidance for determining other mouse *Ttpa* gene genes or that other *Ttpa* genes exist in mouse or have the same function as the *Ttpa* gene disclosed. Limiting claims 1 and 27 to "the endogenous *Ttpa* gene" overcome this rejection.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above, the lack of direction and/or guidance provided by the specification as to how to generate any species of knockout mammal and how to use the claimed knockout with any phenotype, the unpredictability of phenotype of transgenic knockout animals, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the claimed invention with a reasonable expectation of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,8,9,27,34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 27 are indefinite as they refer to a disruption in "an endogenous *Ttpa* gene". It is unclear whether the claims are referring to multiple *Ttpa* genes because it

encompasses multiple species of animals or whether the claims encompass multiple *Ttpa* genes for each species. Note that claims 7 and 30 refer to "the endogenous *Ttpa* gene".

Claims 8,9,34 and 35 encompass animals wherein the gene disruption is only in somatic cells (claims 8 and 34) or only in germ cells (claims 9 and 35). These claims are unclear, as it is not known how to make a "knockout" animal with a gene disruption that is not comprised in all cells of the animal. It is unclear what "a" cell means. Is the claim meant to encompass an animal comprising one recombinant cell in which the *Ttpa* gene has been knocked out only in that one cell? Clarification of what is meant to be encompassed by these claims is necessary.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-5,8-11,27-31 and 34-37 are rejected under 35 U.S.C. 102(a) as being anticipated by Terasawa (Nov. 02,1999, Circulation, Vol. 100, page I-46, abstract number 231).

Terasawa taught a knockout mouse comprising an insertional disruption in the Ttpa gene wherein the insertion comprised the selectable marker gene lacZ. Terasawa generated both homozygous and heterozygous mice that inherently comprised the disruption in both germ cells and somatic cells. It was inherent that the mice comprised the disruption in both somatic and germ cells as mating of animals, chimeric or non-chimeric, to obtain progeny comprising the disruption requires that the disruption be passed through the germ line. Traditional matings would not produce chimeric progeny, therefore the progeny must have comprised the disruption in both somatic and germ cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5,8-11,27-31 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (*Scientific American*, 1994, vol. 270, pp 34-41) in view of Fechner (December, 1999, GenBank Accession # AF218/416).

Capecchi taught a mouse whose genome comprised a disruption in the HoxA-3 gene by insertion of a selective marker gene into the HoxA-3 gene. Capecchi differs from the claimed invention in that the targeting construct does not disrupt the alpha-tocopheral transfer protein (*Ttpa)* gene.

However, at the time the claimed invention was made, Fechner taught the nucleic acid sequence of the mouse *Ttpa* gene and *Ttpa* coding region.

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make a knockout mouse having a disruption in a targeted gene as taught by Capecchi wherein the gene was *Ttpa* gene as taught by Fechner. One of ordinary skill in the art would have been sufficiently motivated to replace the Hox3A gene with the *Ttpa* gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. Furthermore, one of ordinary skill in the art would have been sufficiently motivated to disrupt the *Ttpa* gene to generate an animal model of vitamin E deficiency because alpha-tocopherol transfer protein was known to play an important role in transport of vitamin E.

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph).

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner

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